

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-25 are pending in the application, with claim 1 and 18 being the independent claims.

Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 103 (claims 1-25)

Claims 1-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kempe (U.S. Patent No. 5,514,789) in view of Lyttle *et al.* (Nucleos. Nucleot., 18:1809-1824 (1999)). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

Because the concentrated aqueous ammonia of Lyttle *et al.* comprises a strongly basic conditions, Lyttle *et al.* does not teach away from the invention as asserted by Applicants. In fact, the quotation provided by Applicants in support of their conclusion that Lyttle actually teaches away, when viewed in its proper context, simply explains why a different linker has not been widely adopted for use, and further, provides a context for why the new linker of Lyttle *et al.* is a contribution over the prior art; in other words, Applicants' quoted phrase explains why the findings of Lyttle *et al.* are novel and thus worthy of publication. As such, Applicants' quote does not reverse the relevance of Lyttle's use of strongly basic cleavage conditions to the instant rejection. For these reasons, Applicants' arguments are not convincing, and the claims above stand rejected under 35 U.S.C. § 103(a).

(Office Action, page 4, lines 6-15). Applicants respectfully disagree with the Examiner's

Lyttle teaches away from using harsher reagents, such as gaseous ammonia, the reagent used in Kempe, for the removal reaction. It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983).

Lyttle teaches:

Post synthesis cleavage protocols involve either strongly basic conditions with heating at elevated temperatures for long periods, or the use of alkali metal salts which require additional steps for removal. These limitations have, so far, outweighed the added convenience of one support material for every sequence, and prederivatized supports are still predominantly preferred.

(Lyttle, page 1809, lines 10-14, citation omitted).

The use of strongly basic and harsh reagents was a limitation in the solid-phase synthesis of polynucleotides. Lyttle developed linkers that don't require the harsh reagents used in the prior art, such as alkali metal salts, thus overcoming this limitation. In fact, Lyttle teaches the use of aqueous liquid ammonia as the reagent of choice during removal. "Concentrated aqueous ammonia (0.5 mL) was added and the tube heated in an aluminum hot block at 60 °C for 3 hrs with the PEG polystyrene support, and 8 hrs with the macroreticular polystyrene support. Cleaved products were then evaporated to dryness for subsequent analysis." (Lyttle, page 1813, lines 21-23). Lyttle also teaches: "[a]dditionally, no non-volatile salts or other reagents *besides aqueous ammonia* are needed for deprotection and cleavage, so the crude DNA can be used for a number of applications without the necessity of post-synthetic desalting steps." (Lyttle, page 1823, lines 10-13, emphasis

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supports using a gaseous ammonia reagent. The reagent used in Kempe is, necessarily,

harsher than the reagent used for removal in Lyttle. As a reagent, gaseous ammonia is harsher and more caustic than aqueous ammonium hydroxide. Aqueous ammonium hydroxide solution is formed by the reaction between water and ammonia, which forms ammonium ($^{\oplus}\text{NH}_4$) cations and hydroxide ($^{\ominus}\text{OH}$) anions. Cationic ammonium ions are less basic, less nucleophilic and less harsh than free ammonia (NH_3) because the unshared pair of electrons on ammonia are bound to a hydrogen, giving the ammonium cation a full positive charge. The reduced basicity of ammonium cations, compared to ammonia, make it a milder reagent. "The [ammonium hydroxide] solution is alkaline because much of the dissolved ammonia reacts with water, H_2O , to form ammonium hydroxide, NH_4OH , a *weak base*." (Exhibit A, page 1, lines 13-14, emphasis added).

Lyttle teach that reagents harsher than aqueous ammonium hydroxide are a limitation in the removal process, which should be avoided. Since Lyttle teach that mild reagents, *i.e.*, aqueous ammonium hydroxide, are sufficient for removal, one would not have been motivated to experiment with harsher reagents, such as gaseous ammonia. Since one of ordinary skill in the art would not have been motivated to use gaseous ammonia, it would not have been obvious to use gaseous ammonia at the time the present invention was made. Applicants respectfully submit the rejection under 103(a) is improper and request that it be withdrawn.

Furthermore, claims 24 and 25 of the present application are drawn to the use of pressurized ammonia gas in the removal reaction. Claims 14 and 15 of the present application are drawn to carrying out the removal process at temperatures up to about 150

temperature ammonia. If the milder aqueous ammonium hydroxide reagent is sufficient

for removal of the linker, as taught in Lyttle, one would not have been motivated to use the much harsher pressurized and heated gaseous ammonia reagent. One of ordinary skill in the art would have expected that using pressurized and heated gaseous ammonia would increase the likelihood of side reactions and decomposition, thus complicating the removal procedure taught by Lyttle. Because Lyttle teaches away from using harsh gaseous ammonia in the removal reaction, it is improper to combine the teachings of Lyttle and Kempe. Applicants respectfully submit the rejection under 103(a) is improper and request that it be withdrawn.

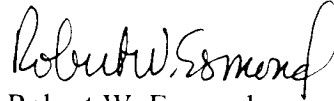
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant(s) therefore respectfully request(s) that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant(s) believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully
requested.

Respectfully submitted,

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